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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,216	12/04/2001	Keith D. Allen	R-881	6807

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,216	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 08/09/2004 has been entered. Claims 1-22 have been cancelled. Claims 23-27 have been added, are pending and are under consideration in the instant office action.

Drawings

A replacement drawing was received on 08/09/04. This drawing is acceptable.

Claim Rejections - 35 USC § 101/112-1st paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 6,7,9,14 and 16-19 as lacking utility as set forth on pages 3-6 of the previous office action mailed 04/06/2004 is maintained as it applies to newly added claims 23-27. Applicant's arguments have been thoroughly considered and are not found to be persuasive. The rejection is maintained for reasons of record.

1) Applicant argues that the claimed transgenic mouse exhibits a specific phenotype resulting from disruption of the TRP6 gene. Applicant argues that the phenotype of increased pain threshold makes the mouse an in vivo model for conditions or disorders related to pain and can be used to discover or develop therapeutic agents useful in modulating abnormal pain sensitivity (page 4, paragraph 3). Applicant asserts

that this utility is specific to the claimed mouse because it is a specific phenotype exhibited by the mouse as a result of the disruption (page 4, last paragraph).

In response, there is no known pain disorder on the record that is characterized by an increased pain threshold. Furthermore, there is no evidence on the record that TRP6 even has a role in pain. There is no evidence on the record that the disclosed results in the hotplate test (pages 53-54) are due to increased pain threshold and not to some other altered characteristic in the mouse (see below). Applicant argues that the claimed phenotypes are specific to the claimed mouse; however, a phenotype specific to the mouse does not render the utility of the mouse specific. The claimed phenotypes are not specific to any disease or disorder such that there would be a specific use for the mice.

2) Applicant argues that the claimed mouse represents a model of the role of the TRP6 gene in pain pathways and that the mice could be used in assays to characterize a variety of potentially therapeutic compounds (page 5, 2nd paragraph).

In response, the only assay the claimed mouse could be used for over the use of a wild-type mouse would be in identifying an agent that reverses the phenotype of increased pain threshold or decreased pain sensitivity. It is not apparent what utility a compound that causes increased pain sensitivity would be. One could argue that use of the claimed mouse to identify compounds that decrease pain threshold offers no utility over wild-type because the TRP6 gene has no correlation to nociception and therefore, an agent that decreases pain threshold or otherwise alters pain perception in the claimed mouse would have the same effect on a wild-type mouse and could have been identified using the wild-type mouse. Furthermore, there is no apparent utility for an agent that decreases pain threshold.

3) Applicant argues that there is no requirement for a correlation between disruption of TRP6 and increased pain threshold and any disease or disorder (page 5, 3rd paragraph).

In response, the specification fails to demonstrate the etiology of the increased pain threshold or to demonstrate adequately that the response of the mouse in the hot plate test is due to increased pain threshold and not to some other physiological or neurological disorder. Importantly, the specification and claims demonstrate that the phenotype has not been characterized in that it cannot be differentiated if the increased response latency in the claimed mice is due to decreased pain sensitivity or increased pain threshold. Furthermore, the observed phenotype of increased response latency in the hot plate test could be the result of a number of other hypotheses that the specification fails to no more rule out than it does the claimed phenotypes. It is just as likely possible that the mice are less sensitive to all stimuli, have slower neurological responses, or thicker dermal layers on the paws and that the response of the mouse in the hot plate test is not specific to the pain pathway. As such, one would not know how to use a compound that ameliorates the response of the claimed mice in the hot plate test because it would not be known what the compound is affecting. Better characterization of TRP6 function that correlates TRP6 to pain sensitivity, a link between the TRP6 gene and a disease or condition, and further testing more definitively correlating the gene disruption specifically to decreased pain sensitivity per se, would all provide a stronger correlation between disruption of TRP6 and decreased pain sensitivity, allowing for credible and specific utility of the claimed mouse. Applicant asserts the utility of the mouse is substantial; however, additional experimentation would be required to determine the

usefulness of the claimed mice because it must be determined whether a compound that ameliorates the increased response latency exhibited by the mice in the hot plate test is effecting pain sensitivity and not some other unidentified characteristic of the mouse that affects its performance in the hot plate test as set forth above. As set forth by the utility guidelines above, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

4) Applicant argues further that the specification sufficiently correlates the phenotype of decreased pain sensitivity to the TRP6 gene disruption and that the Crabbe and Mogil references stating that the genetic background affects performance in behavioral tests and that pain sensitivity is not applicable to the scenario at hand (page 5, last paragraph). Applicant argues that the Crabbe reference does not provide teachings with respect to the hot plate test. Applicant states that a small but significant portion of the TRP6 gene is disrupted making it improbable that the resulting phenotypes are a result of tightly linked gene.

In response, the specification describes increased response latency for the mice and does not definitively correlate or provide any evidence supporting that this result in the hot plate test is a manifestation of increased pain threshold. The Crabbe reference merely demonstrates that genetic background and testing conditions can affect the performance of a mouse in various behavioral tests and this phenomenon should be taken into consideration when interpreting results in a knockout mouse because the genetic background for the knockout differs from that of a wild-type mouse around the knockout locus. The Mogil reference is a more specific example highlighting this phenomenon in behavioral pain assays. The rejection is based on the teachings of Mogil that backgrounds

effects caused by numerous nonspecific polymorphisms and mutations throughout the genome of specific strains can alter the pain sensitivity of a particular strain. Mogil taught a variation in pain sensitivity between various strains. The rejection is based on the fact that, as reported by Mogil, some of these background differences may be linked to the disruption and these loci are selected for in the transgenic but not in the wild-type mice. Without significant backcrossing, background effects must be taken into consideration (see Mogil, specifically page 68, col. 1, lines 11-20; page 78, col. 1, paragraph 3; Table 2). Without a correlation between TRP6 and pain sensitivity or further characterization of TRP6 expression and activity profiles, it would require one of skill in the art undue experimentation to rule out the possibility that the observed phenotype is due to the disruption per se, and is not a result of the genetic background resulting from the process of generating the knockout resulting in different genetic backgrounds for loci linked to the TRP6 between transgenic and wild-type mice. In selecting for the claimed disruption, one is selecting for the 129/OlaHsd chromosome while this selection is not present for WT mice and WT mice are more likely than the claimed transgenic mice to have C57BL/6 loci surrounding the disrupted locus.

Without additional experimentation or correlation between the function of TRP6 and a disease, one would not know what to do with a compound that increases pain sensitivity or threshold or decreases response latency in the hot plate test. Furthermore, the utility of identifying a compound that increases pain sensitivity. Absent further characterization of the mice or the TRP6 gene, it cannot be determined that a compound that affects the claimed decreased response latency and increased pain threshold or decreased pain perception in the hot plate test would have any use. Thus, neither the

claimed mice, the methods of making the mice nor any methods of using the mice have utility.

Enablement

The rejection of claims 23-27 under 35 U.S.C. 112, first paragraph is maintained. Specifically, since the claimed invention is not supported by either a specific and substantial utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The additional aspects of the enablement rejection set forth on pages 6-10 of the previous office action mailed 04/06/04 are withdrawn in light of Applicant's amendments to the claims. Applicant has cancelled previously pending claims. Newly added claims now limit the species of animal to mouse and methods of making the mouse are limited to using a mouse embryonic stem cell. The claims also limit the mice to those exhibiting specific phenotypes. Thus, the newly added claims have overcome the aspects of the enablement rejection set forth on pages 6-10 of the previous office action.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Joe Woitach
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